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The Effect of Dietary Intake of Fruits and Vegetables on the Odds Ratio of Lung Cancer among Yunnan Tin Miners

M R FORMAN,* S X YAO,** B I GRAUBARD,† Y L QIAO,** M McADAMS,‡ B L MAO,** AND P R TAYLOR*

Forman M R (Cancer Prevention Studies Branch, CPRP, DCPC, National Cancer Institute, Executive Plaza North, Room 211C, Bethesda, Maryland 20892, USA), Yao S X, Graubard B I, Qiao Y L, McAdams M, Mao B L and Taylor P R. The effect of dietary intake of fruits and vegetables on the odds ratio of lung cancer among Yunnan tin miners. *International Journal of Epidemiology* 1992; **21**: 437–441.

All newly diagnosed cases of lung cancer (N = 183) among male tin miners of Yunnan Province, China and age-sex matched occupational controls (N = 183 aged 45–79 years) were interviewed within 3 months following cancer diagnosis. The questionnaire included information about usual adult diet as well as employment and smoking histories. Over 95% of cases and controls were current smokers. The 27-item food frequency questionnaire included 11 fruits and vegetables rich in vitamin A and/or carotenoids.

The effect of dietary intake of fruits and vegetables on risk of lung cancer was examined with adjustment for exposures to radon, arsenic, and smoking as previously documented risk factors for lung cancer. Tin miners with reduced intake of yellow and light green vegetables had statistically significant increased odds ratios (OR) of lung cancer (OR = 2.26 and OR = 2.39 for the lowest two quartiles of intake; *P* value for trend = 0.02) among cases compared with controls after multiple logistic regression adjustment for covariates; and this relationship was monotonic. Tin miners with reduced intake of tomatoes had statistically significant increased adjusted OR of lung cancer (OR = 2.64, OR = 3.09, OR = 2.36 for the three lowest quartiles of intake; *P* value for trend = 0.04).

This is the first study to demonstrate a protective effect of vegetable intake versus the strong effects of smoking and occupational exposures on lung cancer risk.

Lung cancer in China accounts for approximately 7.4% of all cancer deaths (8.5% males and 5.9% females), ranking fourth among males and fifth among female cancer deaths, respectively.[1] The highest risk area for lung cancer among males in China is Gejiu City in Yunnan Province, where the Yunnan Tin Corporation (YTC) is located. Lung cancer represents 70–80% of all cancer seen annually among YTC employees and mortality from this cancer is 10 times higher in this area than the rest of the China.[1] Among the recognized risk factors for lung cancer in this population are arsenic and radon exposures;[2,3] tobacco smoking;[2,3] and indoor air pollution.[3]

Dietary intake of fruits and vegetables is inversely associated with the odds ratio (OR) of lung cancer across many populations.[4–11] Only one earlier study examined the association between dietary intake of vitamin A and risk of lung cancer in an industrial setting;[10] however no one has examined the dietary intake of foods rich in vitamin A and carotenoids among cases and occupational controls with extraordinarily strong occupational risk factors for lung cancer in addition to smoking. Therefore, the objective of this paper is to describe the association between dietary intake and the OR of lung cancer among YTC miners, both before and after adjustment for other risk factors.

METHODS

All 183 incident cases of lung cancer among males aged 45–79 years reported to the cancer registration office of the YTC between 1 January 1985 and 31 December 1986 were included in this study. Cases were diagnosed

* Cancer Prevention Studies Branch, CPRP, DCPC, National Cancer Institute, Executive Plaza North, Room 211C, Bethesda, MD 20892, USA.
** Yunnan Tin Miner Corporation, Gejiu City, China.
† Biometry Branch, DCPC, National Cancer Institute, Bethesda, Maryland.
‡ Information Management Systems, Silver Spring, Maryland.

on the basis of X-rays (99%) with sputum cytology (81%) and/or biopsy (34%). Over two-thirds of the cases reported were squamous cell carcinomas of the lung. Occupational controls were chosen systematically by selecting every 20th male from a census of all living workers from the YTC. The controls were matched to cases by date of birth within 5-year age bands. Cases and controls did not differ by usual adult weight and height or by the percentage of current smokers (Table 1). Compared with controls, cases were only slightly less educated and had lower per capita income.

TABLE 1 *Lung cancer incident cases and controls by sociodemographic characteristics and authropometric data. Yunnan Tin Corporation 1985–1986*

	Cases	Controls
No.	183	183
Age (years)	62	62
Self-respondents (%)	80	86
Education (%)		
None	64	53
1–5 years	23	33
5+ years	13	14
Per capita (yuan per month)	122	125
Weight (in kg)	58	58
Height (in cm)	164	164
Current smokers (%)	95	95

A questionnaire was administered to respondents by trained interviewers with information collected on occupation, tobacco smoking, education, residence, prior medical conditions, family history of lung cancer, and diet. Eighty per-cent of cases and 86% of controls answered the questionnaire, with the remainder having surrogate interviews (Table 1). The most common reason for interviewing case surrogates was poor health of the cases, whereas the most common reason for interviewing control surrogates was absence from home at the time of the interview.

Development of Dietary Data

The food frequency questionnaire focused on the usual adult intake of 27 items, 14 of which were specific foods or food groups rich in vitamin A or carotenoids. An initial examination of the distribution of the 14 (vitamin A or carotenoid-containing) foods or food groups by frequency of intake (coded into weekly units over a year) identified five foods with limited intake (i.e. $<25\%$ ate the food more than once a year). These five items were from the meat-fish-egg groups and were excluded from the analysis, while the remaining 9 items were fruits and vegetables (Appendix). Foods that were reported as eaten seasonally were adjusted to reflect annual intake by taking the actual response (in units of times per week during the season) and divided by the number of weeks in the year.

Following discussions with Chinese colleagues about vegetable and fruit eating patterns in this area of China, several algorithms of food intake were developed which assumed that the respondent could report individual intake of each item even among items in mixed dishes. The algorithm combined all items (six vegetables or three fruit items) after taking into account the reported frequency of intake of each item. The recoded data based on these algorithms were referred to as 'total vegetable' or 'total fruit' intake. Also, all five carotenoid-containing vegetables were combined after taking into account the reported frequency of intake and referred to as 'carotenoid vegetables'.

Since the data analysis focused on the relationship between dietary intake and the OR of lung cancer, variables which could potentially bias the reported dietary intake were examined. These included: age at and season of interview; number of meals eaten at home per day, cooking oil by meal preparer; indicators of socioeconomic status; body mass index (adult weight/height^2); respondent (direct or surrogate) status; and alcohol intake. Only number of meals eaten at home per day and indicators of socioeconomic status varied between cases and controls and these were taken into consideration in the multiple variable analyses.

Data Analysis

The analysis proceeded in two phases. In the first phase, we examined the distributions of vitamin A and carotenoid-containing food items and of previously demonstrated risk factors for lung cancer, namely tobacco history, age at diagnosis, arsenic and radon exposures at the YTC. T-tests were computed to determine differences in mean dietary intake of either specific foods or food groups among cases compared to controls. Differences in mean intake were considered statistically significant at a P value of 0.05 or less. Next, each dietary variable was entered into a multiple logistic regression model to estimate the OR of lung cancer after adjustment for the following covariates: total tobacco intake (a summary value for lifetime exposure to water pipe (average liang [50 g] smoked per month times the number of years of reported water-pipe use) and to cigarette smoking in pack-years); age at diagnosis; height; number of meals

at home per day; two socioeconomic indicators (per capita income and the respondent's educational level); and two measures of occupational exposure (summary values estimating radon and arsenic exposure which have been described earlier).[2,3] All variables were treated continuously except for the respondent's educational level which was recorded on the interview form in three categories: 1) no formal schooling, 2) 1–5 years, and 3) 6+ years of schooling with codes of 0, 1, and 2, respectively. The actual (continuous) values for each subject's intake of a specific food were entered into the multiple logistic regression model and a test for trend was computed using PROC LOGIST (SAS).[12]

In the second phase of the analysis, the multiple logistic regression model was analysed with the dietary variable, which was a food item or food group categorized into quartiles of intake with the highest quartile considered the comparison group. The cutoff for each quartile was based on the distribution of each food in the control population.

RESULTS

Compared with controls, cases had significantly lower mean dietary intake of yellow and light green vegetables, tomatoes, oranges, and canteloupes (Table 2). These differences only became significant or approached significance after adjustment for covariates.

Compared with tin miners in the highest quartile of intake of yellow and light green vegetables, those in the lower two quartiles of intake had significantly increased OR of lung cancer after adjustment for covariates (Table 3). Indeed, there was a monotonic relationship between quartiles of yellow and light green vegetable intake and the OR of lung cancer. Compared with tin miners in the highest quartile of intake of tomatoes, those in the lower three quartiles of intake had significantly increased OR of lung cancer. Finally, tin miners with the lowest intake of canteloupes had an increased OR of lung cancer in contrast to those with the highest intake of canteloupes.

Two factors, which might alter dietary recall, namely the percentage of retirees among the cases compared with controls, and the time from diagnosis of lung cancer to interview, were also examined but did not alter the results. Specifically, 53 cases who were retired and their respective controls were included and then removed from the analysis without an effect on the results. Most interviews of cases were conducted within the first 3 months post-diagnosis and therefore the cases were unlikely to be recalling dietary practices after the disease had influenced reponse or actual diet.

TABLE 2 *Mean weekly intake, standard deviation (s.d.), P value (based on T-test) and P value[a] (adjusted) by food/food group and by case and control status: Yunnan Tin Corporation incidence study (N = 366)*

Food group	Case Mean (s.d.)	Control Mean (s.d.)	*P* value	*P* value[a] (adjusted)
Dark green leafy vegetables	1.90 (1.09)	1.86 (1.20)	0.74	0.98
Yellow and light green vegetables	1.19 (0.96)	1.41 (1.13)	0.04	0.02
White vegetables	1.63 (1.13)	1.61 (1.02)	0.86	0.49
Bright orange vegetables	0.09 (0.13)	0.08 (0.10)	0.47	0.63
Sweet green and red peppers	1.00 (0.55)	1.07 (0.65)	0.25	0.27
Tomatoes in season	0.86 (0.39)	0.96 (0.49)	0.04	0.04
Oranges in season	0.13 (0.12)	0.16 (0.20)	0.13	0.03
Canteloupes	0.07 (0.08)	0.09 (0.15)	0.15	0.06
Other fruits	0.28 (0.20)	0.29 (0.30)	0.47	0.81
Total vegetable intake	6.62 (2.81)	6.95 (3.09)	0.29	0.11
Total fruit intake	0.48 (0.30)	0.54 (0.53)	0.15	0.26

[a] *P* value from the multiple logistic regression model using the actual values for each food item after adjustment for other risk factors.

DISCUSSION

Among a population of tin miners with exposure to radon, to arsenic, and tobacco as risk factors for lung cancer, dietary intake of certain fruits and vegetables was inversely associated with the OR of lung cancer. Specifically, reduced intake of one food group (yellow and light green vegetables) and of one food (tomatoes) were statistically significantly associated with increased OR of lung cancer after adjustment for covariates. Moreover there was evidence of a dose-response relation between quartiles of yellow and light green vegetable intake and the OR of lung cancer. These results should be interpreted with caution since many tests have been performed without any adjustment for multiple comparisons such as the Bonferroni adjustment.

The effect of dietary intake of fruits and vegetables on the OR of lung cancer was limited to yellow and light green vegetables and to tomatoes. The yellow and light green vegetables included specific carotenoid-rich

TABLE 3 *Adjusted odds ratio (OR) of lung cancer with the 95% confidence interval (95% CI) by quartile of intake of vitamin A and carotenoid containing foods: multiple logistic regression model (N = 358)*

Variable	Cases and controls		
	Quartiles	OR	(95% CI)
Total fruit intake	(4)	1.00	
	3	0.72	(0.35–1.45)
	2	0.80	(0.40–1.59)
	1	0.91	(0.48–1.74)
Total vegetable intake	(4)	1.00	
	3	2.00	(1.02–3.91)
	2	1.39	(0.70–2.79)
	1	1.68	(0.85–3.29)
Carotenoid vegetables	(4)	1.00	
	3	0.99	(0.51–1.95)
	2	1.67	(0.85–3.26)
	1	1.48	(0.76–2.88)
Dark green leafy vegetables	(4)	1.00	
	3	0.72	(0.38–1.34)
	2	0.67	(0.34–1.32)
	1	0.82	(0.41–1.61)
Yellow and light green vegetables	(4)	1.00	
	3	1.28	(0.57–2.87)
	2	2.26	(1.01–5.05)
	1	2.39	(1.15–4.96)
Bright orange vegetables	(4)	1.00	
	3	0.98	(0.44–2.21)
	2	0.93	(0.45–1.94)
	1	1.10	(0.54–2.23)
Green and red peppers	(4)	1.00	
	3	0.94	(0.13–6.57)
	2	1.24	(0.68–2.28)
	1	1.24	(0.71–2.18)
Tomatoes	(4)	1.00	
	3	2.64	(1.20–5.85)
	2	3.09	(1.36–7.04)
	1	2.36	(1.04–5.33)
Canteloupes	(4)	1.00	
	3	1.59	(0.75–3.38)
	2	2.04	(0.93–4.49)
	1	2.03	(1.01–4.07)

foods, most notably green beans rich in beta-carotene and lutein, and squashes rich in lutein, beta-cryptoxanthin, and beta-carotene.[13] Tomatoes have a high concentration of lycopene. These carotenoids are detected in human plasma following consumption and only one, beta-carotene has provitamin A activity. Thus consumption of vegetables rich in carotenoids with and without provitamin A activity may be associated with lower cancer risk in this and other populations.[14]

Consumption of dark green vegetables, which are also rich in vitamin A, carotenoids, folate and other micronutrients, have previously been associated with a protective effect for lung cancer,[15] but it was not associated with a reduced OR of lung cancer here. This may be due to the high intake of dark green vegetables by the Chinese (78% consumed them at least twice weekly). Other foods, such as carrots, which have been inversely associated with the OR of lung cancer, were not eaten by Gejiu City residents of China.[6]

The extraordinary high rate of current tobacco smoking (95%) across cases and controls reduced the chances of detecting an association between tobacco smoking and lung cancer. An analysis of the interaction between cigarette smoking and dietary intake of (specific) fruits and vegetables did not reveal any association with lung cancer risk. Indeed, the protective effect of carotenoid intake on the risk of lung cancer among current male smokers has been inconsistent in previous research, with both negative[4,9] and positive studies.[5,7,8,11,15] The inconsistency might be partially due to mixing recent exsmokers with current smokers.[7,15] Exsmokers may have a lifetime exposure to cigarette smoke which might differ from current smokers and may have terminated smoking with a concomitant dietary change leading to a greater chance of demonstrating a protective effect of carotene intake on the OR of lung cancer. Since most study subjects had substantial occupational exposure to radon and arsenic as well as to tobacco smoke, it is remarkable that a protective effect for selected dietary constituents was still observed.

The percentage of surrogate interviews was low (i.e. 20% and 14% of cases and controls, respectively). Moreover surrogate response bias is highly improbable in this population for the following reasons: 1) the percentage of foods with 'unknown' frequency of intake was higher among the index cases than the surrogate respondents; and 2) most of the unknown responses were in food groups which have not been associated with cancer risk (e.g. steamed bread).

In sum, dietary intake of specific fruits and vegetables was inversely associated with the OR of lung cancer among a population of lung cancer cases compared with occupational controls. These results support the idea that, even with exposure to numerous carcinogens, ingestion of foods high in vitamin A and/or carotenoids are associated with a reduced risk of lung cancer. Whether intakes of pharmaceutical

doses of specific micronutrients e.g. beta-carotene can ameliorate the adverse effects of cigarette smoke and occupational exposures on lung cancer risk are currently being investigated in randomized intervention trials.[16,17]

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APPENDIX

Foods listed as examples for each food group in the food frequency questionnaire.

Dark green leafy vegetables: spinach, Chinese cabbage.

Yellow and light green vegetables: green beans, squashes, bean sprouts.

White vegetables: cauliflower, eggplant.

Bright orange vegetables: orange winter squash.

Sweet green and red peppers.

Tomato in season.

Mandarin orange in season.

Canteloupe melon in season.

Other fruits: apples, pears, bananas, pineapples.